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Measures of sleep-wake patterns and risk of mild cognitive impairment or dementia in older women

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Abstract

Objective—Sleep disturbances are common in older adults. Little is known about the sleep of cognitively-intact older adults and its relationship to subsequent cognitive impairment. The objective of this study was to examine the association between objective sleep-wake measures and risk of incident cognitive impairment.

Design—Prospective cohort study

Setting—Four U.S. sites

Participants—1245 women (mean age 82.6 years) without dementia participating in the Study of Osteoporotic Fractures who completed actigraphy at baseline visit and comprehensive cognitive assessment at follow-up.

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Supplemental Digital Content

Supplementary Tables 1-4 (15-0626 SOF actigraphy and cognitive decline_suppl tables AJGP.docx)

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Measurements—Examine the association between sleep-wake patterns measured by actigraphy and risk of incident mild cognitive impairment (MCI) and dementia.

Results—A total of 473 (38%) women developed cognitive impairment during an average (SD) follow-up of 4.9 (0.6) years; 290 (23.3%) developed MCI and 183 (14.7%) developed dementia. After controlling for multiple potential confounders, women in the lowest quartile of average sleep efficiency (<74%) had a 1.5-fold higher odds of developing MCI or dementia compared to women in the highest quartile of sleep efficiency (>86%)(OR Q1 vs. Q4 1.53, 95% CI 1.07, 2.19; Wald $\chi 2$ [1, N=1223]=5.34 for p for trend=0.03). Longer average sleep latency, but not total sleep time, was also associated with higher odds of developing cognitive impairment. Greater variability in both sleep efficiency and total sleep time was associated with an increased odds of developing MCI or dementia.

Conclusions—Lower average sleep efficiency, longer average sleep latency, and greater variability in sleep efficiency and total sleep time are associated with increased odds of developing cognitive impairment. Further research is needed to explore the mechanisms underlying these associations.

Keywords

cognitive aging; sleep disorders; older women

INTRODUCTION

Cognitive impairment and dementia represent a significant burden in the aging population; approximately 5 million adults aged 65 years and older in the United States had Alzheimer's disease dementia in 2010,(1) with the number of people with this disease expected to increase dramatically as the population ages. Significant sleep disruption is often observed in patients with dementia(2) and is believed to be related to the neurodegenerative process. Less is known about the sleep of cognitively-intact older adults and its relationship to subsequent cognitive decline. The existing prospective data examining the association between sleep disturbances and risk of incident cognitive impairment or dementia is largely based on self-report of sleep(3-8) and has yielded mixed findings, with variable associations between insomnia complaints, daytime sleepiness, total self-reported sleep time, and subsequent cognitive decline.

Evidence that objective measures of sleep quality are associated with subsequent cognitive impairment is limited. One prospective study of community dwelling older men without evidence of dementia found that lower sleep efficiency and greater nighttime wakefulness, but not total sleep time, as measured by actigraphy, were associated with subsequent decline in executive function as measured by the Trails B test.(9) Higher levels of sleep fragmentation as measured using a novel metric derived from actigraphy was associated with an increased risk of Alzheimer's disease over an average follow-up of 3.3 years in another cohort of community dwelling older adults without dementia.(10)

To test the hypothesis that poor sleep, assessed objectively using wrist actigraphy, is associated with increased risk of decline in cognitive function, we used data from 1245 older

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women without dementia participating in the Study of Osteoporotic Fractures, a long-term prospective cohort study. Participants completed wrist actigraphy to assess sleep-wake patterns at a baseline exam, as well as an expanded cognitive assessment an average of 4.9 years later. Specifically, we hypothesized that more fragmented sleep and short sleep are associated with increased risk of the development of mild cognitive impairment (MCI) or dementia.

METHODS

Participants

Women were participants in the Study of Osteoporotic Fractures (SOF), a longitudinal cohort study of community-dwelling women age 65 years or older, recruited from 4 study centers in Baltimore, MD; Minneapolis, MN; Portland, OR; and the Monongahela Valley near Pittsburgh, PA.(11) Women were excluded if they had a bilateral hip replacement or were unable to walk without assistance. The baseline SOF exams were conducted from 1986-1988, when 9704 Caucasian women were recruited; minority women were initially excluded due to their low incidence of hip fracture. However, in 1997-1998 662 African-American women were enrolled. For this analysis, we included participants who completed wrist actigraphy during SOF Visit 8 (2002-2004) and an expanded cognitive assessment during SOF Visit 9 (2006-2008), which included participants from 3 of the original 4 sites (MN, OR, and PA).

Of the 2570 women with actigraphy data at Visit 8 at the three clinical centers, 1785 women participated in Visit 9. Of these, 1284 provided sufficient data for adjudication of cognitive impairment status. The cognitive status for 12 of these women was adjudicated as indeterminate and they were excluded from the present analysis. We also excluded 27 women who were identified as possibly having cognitive impairment at Visit 8 based on use of dementia medications (n=8), self-report of a diagnosis of dementia (n=7), or a Mini-Mental State Examination (MMSE) score of <24 (n=16), with some overlap of criteria. The remaining 1245 women are included in the present analysis.

The institutional review boards on human research approved the study at each institution and all participating women provided informed consent.

Measures of sleep-wake patterns

Actigraphy data were collected with the Sleep-Watch-O (Sleep-Watch-O®, Ambulatory Monitoring, Inc., Ardsley, NY) actigraph, a small device worn on the nondominant wrist. Movement is measured by a piezoelectric linear accelerometer (sensitive to 0.003 g and above), which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and summarized over 1-minute epochs. Actigraphy has been shown to provide a reliable estimate of sleep/wake activity.(12)

Participants were instructed to wear the actigraph continuously for a minimum of 3 days and nights (i.e., 72 hours). They were also asked to keep a sleep diary in which they recorded whether the actigraph recording represented their normal sleep/wake patterns as well as their time to bed, time of final arising, and any times the actigraphy was removed. Sleep diaries

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were used to aid in editing the actigraph data. Points were placed on the computer file to mark the intervals the participants were in bed trying to sleep and the times the device was removed based on time points reported on their diary. Actigraph removals listed on the diary were deleted from the analysis. If the data suggested the actigraph had been removed but no information was collected on the diary, these time points were deleted from the analysis. ActionW-2 software (Ambulatory Monitoring, Inc.) was used to analyze actigraphy data collected in the proportional integration mode.(13) This sleep scoring algorithm calculates a moving average, which takes into account the activity level immediately before and after the current minute to determine whether a given time point should be coded as sleep or wake. Details of the actigraphy scoring methods used in the SOF study have been published elsewhere.(14)

Sleep-wake parameters examined in this analysis were total sleep time per night (TST) (total hours slept while in bed), sleep latency (SL) (amount of time until sleep onset, defined as when the participant achieved sleep for 20 continuous minutes after getting into bed), and two measures of sleep fragmentation: sleep efficiency (SE) (percentage of time participant was sleeping while in bed) and time awake after sleep onset (WASO) (the total minutes of time scored as awake from sleep onset to the end of the sleep interval). For our primary analyses, a given sleep parameter averaged over all nights was used as the predictor. In addition, we examined the standard deviation of each sleep parameter over all nights as a predictor to evaluate the relationship between night-to-night variability of each sleep parameter and cognitive function.

Cognitive assessment and adjudication

The shortened Mini-Mental State Examination (MMSE)(15) (a test of global cognition) and Trails B(16) (a test of executive function) were administered at all clinic visits including at baseline (i.e. Visit 8). At the follow-up visit (Visit 9, approximately 5 years later), an expanded neuropsychological test battery was administered, including Trails B, the Modified Mini-Mental State Examination (3MS)(17), the California Verbal Learning Test (CVLT) (second edition short form)(18), Digit Span (from the Wechsler Adult Intelligence Scale-Revised)(19), and category and verbal fluency tests.(20)

Cognitive impairment was determined in a 2-step process that has been described elsewhere.(21) Women were screened for cognitive impairment at Visit 9 using 1 or more of the following criteria: 1) score <88 on the 3MS; 2) score <4 on the California Verbal Learning Test delayed (10 minute) recall; 3) score ≥3.6 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a questionnaire designed to assess cognitive decline and dementia in elderly people completed by a relative or friend(22); 4) self-reported previous dementia diagnosis; or 5) nursing home or personal care home residence.

The women who screened positive had their cognitive status adjudicated by a panel of clinical experts, which included a neurologist, 2 neuropsychologists, and a geropsychologist, who were blinded to the actigraphy results. The remaining women who screened negative were considered to be cognitively normal. Information used for assessment included the Visit 9 neuropsychological battery scores, IQCODE, prior cognitive test scores, years of education, medical history, medications, Geriatric Depression Scale score (GDS), and

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functional status. The diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DMS-IV) criteria.(23) Mild cognitive impairment (MCI) was diagnosed using a modified Petersen Criteria.(24,25) Participants were classified as having cognitive impairment if they had a diagnosis of MCI or dementia.

Other Measurements

Participants completed a questionnaire and were asked about self-reported health, education, smoking status, alcohol use, walking for exercise, and living situation. A medical history was obtained, including a history of stroke, diabetes, Parkinson's disease, non-skin cancer, chronic obstructive pulmonary disease, or coronary heart disease (angina/myocardial infarction), congestive heart failure, and hypertension. Functional status was assessed by collecting information on 6 instrumental activities of daily living (IADLs), which included walking 2 to 3 blocks on level ground, climbing up to 10 steps, walking down 10 steps, preparing meals, doing heavy housework, and shopping for groceries or clothing.(26,27)

The 15-item Geriatric Depression Scale (GDS) was used to assess depressive symptoms.(28) Body weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. All measurements were collected at visit 8, the baseline examination for this analysis.

Participants were asked to bring in all medications used within the preceding 30 days. All prescription and nonprescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).(29) Drug categories included antidepressants, benzodiazepines, and prescription sleep medications (non-benzodiazepine, non-barbiturate sedative hypnotics).

Statistical analysis

Characteristics known to be related to sleep or cognitive function were summarized by quartile of averaged sleep efficiency across all nights using means and standard deviations for continuous data and counts and percentages for categorical data. We compared characteristics across quartiles of sleep efficiency, using analysis of variance for normally distributed continuous variables; a Kruskall-Wallis test for skewed data; and a chi-square test for categorical data. Similar comparisons were made for the other predictors examined (data not shown).

We then used logistic regression to examine the association between the objective sleep measures and risk of developing mild cognitive impairment or dementia, with a separate model for each predictor. The odds ratio (OR) and 95% confidence interval (CI) for each outcome was calculated across quartile of each sleep predictor. For averaged total sleep time, the referent group was the middle two quartiles due to the U-shaped relationship between total sleep time and cognitive function previously reported.(7,30,31) For averaged sleep efficiency, the referent group was the highest quartile; for averaged sleep latency, the referent group was the quartile with the lowest sleep latency; for averaged WASO, the referent group was the quartile with the lowest WASO. Tests for a linear trend across quartiles were performed by including each predictor (ordinal variable, four levels) as an

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independent variable in models. Minimally adjusted models controlled for age, race, clinic, and education. Models were further adjusted by covariates that were associated with one or more of the sleep predictors in univariate analyses or the outcome of MCI or dementia in age-adjusted models at $p < 0.10$ (full multivariate model: age, race, clinic, education, body mass index, depressive symptoms, comorbidities, IADL impairments, smoking, alcohol, exercise, living alone, self-reported health status, use of antidepressants, benzodiazepines, and prescription sleep medication use). We also explored the association between the variability of the actigraphic measures over the days of monitoring and risk of incident MCI or dementia by examining the standard deviation of each sleep measure across all days of recording in the models. These variables were also examined as quartiles, with the lowest quartile used as the reference category.

RESULTS

Baseline characteristics

Among the 1245 women (mean age 82.6 years, SD 3.3) in the analytical sample, actigraphic data were collected for an average (SD) of 3.6 (0.7) 24-hour periods. Median (interquartile range) of average total sleep time was 6.91 (6.11-7.51) hours; median (interquartile range) averaged sleep efficiency was 81.8% (74.4-86.3%); median (interquartile range) averaged WASO was 58.3 (39.3-85.8) minutes; and median (interquartile range) averaged sleep latency was 28.8(17.3-47.5) minutes. Characteristics of participants by quartile of averaged sleep efficiency are shown in Table 1. Compared to those in higher quartiles, those with lower sleep efficiency (SE quartile 1) were on average younger and had higher BMI, more comorbidities, higher number of depressive symptoms, and more IADLS impairments. They were more likely to be African-American and to report worse health status. Characteristics of participants by quartile of total sleep time, sleep latency, and WASO appear in Supplementary Tables 1-3.

911 women who did not have evidence of cognitive impairment at Visit 8 and were alive at Visit 9 did not complete the Visit 9 cognitive assessment and therefore were not included in this analysis. Characteristics of these women compared to the women in our analytic cohort appear in Supplementary Table 4. Women not included in this analysis were older on average by about one year, had a slightly lower MMSE score on average, and did have lower average sleep efficiency, higher average WASO, and higher average variability in total sleep time and sleep efficiency.

Averaged sleep measures and MCI/dementia

A total of 473 (38%) women developed cognitive impairment during an average (SD) follow-up of 4.9 (0.6) years; 290 (23.3%) developed MCI and 183 (14.7%) developed dementia.

Lower averaged sleep efficiency was associated with greater odds of developing MCI or dementia (Table 2). In a minimally adjusted model (covariates of age, race, clinic, and education), women in quartile (Q) 1 (<74.39%) had a 1.55-fold higher risk of developing MCI or dementia compared with women in Q4 (referent group, ≥86.261). After adjustment

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for multiple potential confounders in the full model, (i.e., age, race, clinic, education, BMI, number of depressive symptoms, comorbidities, number of IADL impairments, smoking status, alcohol use, exercise, living alone, self-reported health status, antidepressant use, benzodiazepine use, and prescription sleep medication use), results were similar: women in Q1 compared to Q4 had a 1.53 higher risk of developing cognitive impairment. Longer sleep latency was also associated with an increased odds of developing MCI or dementia. In the minimally adjusted model, women in quartile 4 (>47.5 min) had a 1.4-fold higher risk of developing MCI or dementia compared with women in Q1 (referent group, <17.25 min). In the full multivariate model, results were similar similar (Wald $\chi 2$ [1, N=1223]=4.07 for p for trend=0.04). Total sleep time was not associated with the odds of developing cognitive impairment in either the minimally adjusted model or full multivariate model, nor was the number of minutes of wakefulness after sleep onset (Table 2).

Variability in sleep measures and MCI/dementia

Greater variability in sleep efficiency was associated with risk of developing MCI and dementia (Table 3). In both a minimally adjusted model and the full multivariate model, women in Q4 (most variability in sleep efficiency over the all nights) had a 1.9-fold higher risk of developing MCI or dementia compared to those in the lowest quartile (full multivariate model). Variability in total sleep time was also associated with an increased risk of developing MCI or dementia: women in Q4 of total sleep time variability had a 1.4-fold higher risk compared to those in the lowest quartile of variability for the full multivariate model. Variability in time spent awake after sleep onset (WASO) and sleep latency were not related to risk of developing MCI and dementia.

CONCLUSIONS

We found that lower averaged sleep efficiency and longer averaged sleep latency, but not total sleep time or nighttime wakefulness, were associated with a higher odds of developing cognitive impairment. These findings persisted after controlling for multiple potential confounders. Women with the lowest sleep efficiency had a 1.5 greater odds of developing MCI or dementia over the 4.9 years of follow-up, while women with the longer sleep latencies had a 1.4 greater odds of cognitive decline. In addition, we found that variability in sleep efficiency and total sleep time were also associated with increased odds of developing cognitive impairment.

Older adults with dementia have been well documented to experience disturbed sleep, (32-34) thought to be due to changes associated with the neurodegenerative process, as well as reflective of comorbidities.(35,36) Sleep is disturbed early in the neurodegenerative process and sleep disturbances are observed in the presence of MCI.(2,37) However, it is more uncertain if sleep disturbances increase risk for future development of cognitive impairment.

Potential biologic links between sleep disturbances and cognitive decline have been identified. The accumulation of amyloid-beta in the brain extracellular space is an important event in the pathogenesis of AD. Both the sleep-wake cycle and orexin, a neurotransmitter that regulates wakefulness, have been shown to play a role in regulating amyloid-beta

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dynamics.(38) The effects of sleep deprivation and orexin modulation have been examined in wild-type mice and human amyloid precursor protein transgenic mice, which express a mutated form of *hAPP*.(38) The quantity of amyloid-beta measured in brain interstitial fluid was shown to correlate with the amount of wakefulness and with orexin dynamics.(38) Chronic sleep restriction increased amyloid-B plaque formation in the amyloid precursor protein transgenic mice.(38) Other recent work suggests that sleep affects the ability of the brain to remove potentially toxic biomolecules that accumulate with normal neuronal function, including beta-amyloid.(39) Clearance of these toxic waste products is as much as two-fold faster in sleep than in waking hours.(39) In addition, in aged rats, chronic sleep restriction leads to alterations in Ca++ signaling and abnormalities of synaptic plasticity in the hippocampus, an area of the brain that plays an important role in memory and where early abnormalities are seen in Alzheimer's disease.(40-42) Recent studies in humans have linked lower sleep efficiency and greater WASO measured by actigraphy as well as poorer sleep quality and shorter sleep duration measured by self-report to greater amyloid deposition.(43,44)

In humans, cross-sectional studies have reported associations between sleep disruption and cognitive impairments in community-dwelling older adults. Of those that have examined objective measures of sleep and cognitive function, sleep fragmentation, as measured by a variety of parameters, has been associated with poorer cognition.(45-47) However, due to the cross-sectional nature of this work, conclusions regarding the direction of these associations cannot be made. Much of the limited prospective data examining the association between sleep disturbances and risk of incident cognitive impairment have focused on self-reported total sleep time (TST) and sleep quality.(3-8) One prospective study of community dwelling older adults without dementia that did objectively measure sleep utilizing actigraphy found that higher levels of sleep fragmentation were associated with an increased risk of Alzheimer's disease(10); however, that study did not measure other sleep parameters, such as sleep efficiency, WASO, or total sleep time. Another prospective study(9) found that lower sleep efficiency and greater nighttime wakefulness as measured by actigraphy was associated with an increased risk of subsequent decline on a measure of executive function; however, this work did not measure outcomes of mild cognitive impairment or dementia, as we did in the present study.

Although we did observe an association between sleep efficiency and incident cognitive impairment, we did not observe an association between total sleep time and incident cognitive impairment. Animal work has suggested that decreased total sleep time may potentially play a role in the accumulation of beta-amyloid in the brain(38,39) and Spira et al(44) found that shorter self-reported total sleep time was associated with greater beta-amyloid burden cross-sectionally. Our prospective data based on actigraphic measures suggests that reduced sleep efficiency, rather than total sleep time, is more strongly associated with incident cognitive impairment.

We found that variability in sleep efficiency and total sleep time were also associated with increased odds of developing MCI or dementia. Greater variability in sleep efficiency and WASO has been correlated with poorer performance on a new associative learning task(48) in older adults. Little work to date has examined variability in these sleep parameters.

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However, increased daily variation in these parameters may be tied to disruptions in the alignment of circadian rhythms, which have been associated with a range of health outcomes.(49) Future studies should explore whether this variability is an early symptom of cognitive changes and whether such variability reflects weakening of circadian rhythms.

Lower sleep efficiency and increased variability of sleep parameters in adults without significant cognitive impairment may be associated with the development of later cognitive impairment due to early neurodegenerative changes not yet manifesting as cognitive impairment. Alternatively, these alterations in sleep may have a causal relationship with the later development of cognitive impairment. Further research will be important to better identify the mechanisms underlying this association.

This research has several strengths. We examined a large cohort of community-dwelling women who were not selected on the basis of sleep or cognitive complaints. We examined objective measures of sleep using actigraphy, adjusted for multiple important confounders, and utilized a rigorous adjudication process for the outcomes of MCI and dementia. We excluded participants with probable dementia or cognitive impairment at Visit 8, the baseline visit for this analysis, and so were able to evaluate for risk of incident MCI and dementia. There are, however, several limitations. The cognitive assessment at Visit 8 was less robust than at follow-up and, as a result, we cannot exclude the possibility that some women included in the analysis had MCI or dementia at Visit 8. If women who had cognitive impairment at Visit 8 were included in this analysis, it is possible that they already were experiencing changes in their sleep-wake cycle and therefore could have biased our results. In addition, to be included in our analysis, women had to have completed actigraphy at Visit 8 and a cognitive assessment at Visit 9; women who did not complete Visit 9 may have been more likely to have had cognitive impairment at follow-up. On average, these women not included in the analysis had lower sleep efficiency, higher WASO, and more variability in their sleep parameters than those women included in the analysis, potentially attenuating our observed association between actigraphic measurements and incident cognitive impairment. Due to the observational nature of the study, we cannot exclude residual confounding that may explain our observed results. Lastly, because the cohort was restricted to older, primarily Caucasian women, we cannot generalize our findings to other populations, such as men, younger women, or a more diverse population.

Further research will be important to better identify the mechanisms underlying the observed associations between these sleep parameters and the development of MCI and dementia. Identifying older adults with sleep disturbances may be useful prognostically to identify those at higher risk for cognitive impairment. Future work could examine whether interventions to improve sleep efficiency and reduce variability in sleep parameters improve cognitive outcomes in older adults.

Supplementary Material

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Table 1

Baseline Characteristics of Participants for Overall Cohort by Averaged Sleep Efficiency

Characteristic	Overall (N=1245)	Quartile[a] of Averaged Sleep Efficiency, %				P-value[b]	χ^2 [d.f, N] or F-value [d.f]
		Q1 (N=311)	Q2 (N=311)	Q3 (N=311)	Q4 (N=312)		
Age, years, mean (SD)	82.63 (3.32)	82.2 (3.70)	82.63 (3.36)	82.91 (3.27)	82.77 (2.85)	0.04	F = 2.73 [3, 1241]
Caucasian, n (%)	1109 (89.08)	243 (78.14)	276 (88.75)	292 (93.89)	298 (95.51)	<0.001	χ^2 = 58.99 [3, 1245]
Self-reported health status, n (%)						<0.001	χ^2 = 23.76 [6, 1245]
Poor/very poor	16 (1.29)	7 (2.25)	6 (1.93)	1 (0.32)	2 (0.64)		
Fair	225 (18.07)	72 (23.15)	67 (21.54)	40 (12.86)	46 (14.74)		
Good/excellent	1004 (80.64)	232 (74.60)	238 (76.53)	270 (86.82)	264 (84.62)		
Education, years, mean (SD)	12.88 (2.57)	12.73 (2.54)	12.9 (2.54)	12.86 (2.66)	13.03 (2.53)	0.54	F = 0.71 [3, 1241]
Lives alone, n (%)	734 (58.96)	181 (58.20)	184 (59.16)	180 (57.88)	189 (60.58)	0.90	χ^2 = 0.57 [3, 1245]
Average drinks per week, mean (SD)	1.12 (2.87)	1.29 (3.67)	1.02 (2.48)	1.03 (2.35)	1.16 (2.79)	0.70	χ^2 = 1.42 [3, 1245]
Never smoked, n (%)	824 (66.18)	193 (62.06)	200 (64.31)	207 (66.56)	224 (71.79)	0.21	χ^2 = 8.46 [6, 1245]
Current antidepressant use, n (%)	131 (10.52)	42 (13.50)	29 (9.32)	28 (9.00)	32 (10.26)	0.24	χ^2 = 4.20 [3, 1245]
Current benzodiazepine use, n (%)	84 (6.75)	27 (8.68)	19 (6.11)	20 (6.43)	18 (5.77)	0.46	χ^2 = 2.57 [3, 1245]
Current prescription sleep medication use, n (%)	14 (1.12)	7 (2.25)	2 (0.64)	3 (0.96)	2 (0.64)	0.18	χ^2 = 4.92 [3, 1245]
# of medical conditions[c] (0-8), mean (SD)	1.39 (1.11)	1.59 (1.16)	1.41 (1.08)	1.31 (1.12)	1.25 (1.04)	<0.001	χ^2 = 16.78 [3, 1244]
GDS score (0-15), mean (SD)	1.9 (2.21)	2.34 (2.45)	1.93 (2.29)	1.62 (1.92)	1.73 (2.10)	<0.001	χ^2 = 21.21 [3, 1243]
IADL impairments (0 - 6), mean (SD)	1.12 (1.57)	1.51 (1.76)	1.11 (1.52)	1.11 (1.59)	0.76 (1.27)	<0.001	χ^2 = 32.33 [3, 1245]
BMI, kg/m^2, mean (SD)	27.5 (4.82)	28.92 (5.26)	27.67 (5.01)	26.89 (4.47)	26.53 (4.14)	<0.001	F = 15.40 [3, 1235]
Walks for exercise, n (%)	516 (41.88)	119 (38.89)	129 (41.75)	142 (45.95)	126 (40.91)	0.34	χ^2 = 3.35 [3, 1232]
MMSE (0-30), mean (SD)	28.49 (1.36)	28.24 (1.43)	28.48 (1.35)	28.62 (1.36)	28.61 (1.27)	0.001	χ^2 = 15.97 [3, 1245]
Visit 9 3MS (0-100), mean (SD)	88.10 (9.67)	86.58 (9.83)	88.46 (9.82)	87.81 (10.75)	89.56 (7.86)	<0.001	χ^2 = 19.81 [3, 1244]
Visit 9 cognitive status, n (%)						0.03	χ^2 = 14.04 [6, 1245]
Normal	772 (62.01)	177 (56.91)	193 (62.06)	190 (61.09)	212 (67.95)		
MCI	290 (23.29)	83 (26.69)	63 (20.26)	74 (23.79)	70 (22.44)		
Dementia	183 (14.70)	51 (16.40)	55 (17.68)	47 (15.11)	30 (9.62)		

Abbreviations: GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; BMI, body mass index; MMSE, Mini-Mental State Examination; 3MS, Modified Mini-Mental State Examination; MCI, Mild Cognitive Impairment

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[a] Quartile cutpoints: 74.39, 81.84, 86.26

[b] p-values for continuous variables are from ANOVA (F-statistic) for normally distributed variables, a Kruskall-Wallis test (χ^2) for skewed data; p-values for categorical are data from a chi-square test for homogeneity (χ^2).

[c] Select medical conditions include history of cancer, stroke, diabetes, Parkinson's disease, chronic obstructive pulmonary disease, congestive heart failure, hypertension and coronary heart disease (angina/myocardial infarction)

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Table 2

Averaged Objective Sleep Measures and Odds of Dementia or MCI

	Outcome = MCI or Dementia vs. Normal			
	Minimally Adjusted[a]		Multivariate Adjusted[b]	
Predictor (average over all nights)	**OR (95% CI)**	**Wald χ^2 [1, N=1245], p-value**	**OR (95% CI)**	**Wald χ^2 [1, N=1223], p-value**
Total Sleep Time, hours				
Q1 (<6 hrs, 7 min)	0.92 (0.69-1.24)	0.30, p = 0.59	0.85 (0.63-1.16)	1.02, p = 0.31
Q2-3 (6 hrs to <7.5 hrs)	1.00 (reference)	- -	1.00 (reference)	- -
Q4 (≥7.5 hrs)	1.00 (0.75-1.33)	0.00, p = 0.98	0.93 (0.69-1.25)	0.26, p = 0.61
Sleep Efficiency, %				
Q1 (<74.39)	1.55 (1.10-2.18)	6.28, p = 0.01	1.53 (1.07-2.19)	5.34, p = 0.02
Q2 (74.39 to <81.84)	1.31 (0.93-1.83)	2.37, p = 0.12	1.33 (0.94-1.89)	2.53, p = 0.11
Q3 (81.84 to <86.26)	1.34 (0.96-1.88)	2.91, p = 0.09	1.38 (0.97-1.95)	3.25, p = 0.07
Q4 (≥86.26)	1.00 (reference)	- -	1.00 (reference)	- -
p-trend		5.40, p = 0.02		4.54, p = 0.03
Wake After Sleep Onset, minutes				
Q1 (<39.25)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (39.25 to <58.33)	1.21 (0.87-1.70)	1.30, p = 0.26	1.27 (0.90-1.80)	1.87, p = 0.17
Q3 (58.33 to <85.75)	1.16 (0.83-1.62)	0.75, p = 0.39	1.14 (0.80-1.61)	0.51, p = 0.47
Q4 (≥85.75)	1.21 (0.86-1.69)	1.18, p = 0.28	1.16 (0.81-1.66)	0.66, p = 0.42
p-trend		0.89, p = 0.35		0.33, p = 0.57
Sleep Latency, minutes				
Q1 (<17.25)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (17.25 to <28.75)	1.08 (0.77-1.52)	0.21, p = 0.65	1.12 (0.79-1.59)	0.41, p = 0.52
Q3 (28.75 to <47.50)	1.29 (0.92-1.80)	2.16, p = 0.14	1.37 (0.97-1.93)	3.19, p = 0.07
Q4 (≥47.50)	1.42 (1.01-1.99)	4.14, p = 0.04	1.37 (0.96-1.94)	3.04, p = 0.08
p-trend		5.06, p = 0.03		4.07, p = 0.04

A separate model was run for each predictor.

[a] Adjusted for age, race, clinic and education

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[b] Adjusted for age, race, clinic, education, body mass index, number of depressive symptoms, comorbidities, number of IADL impairments, smoking status, alcohol use, exercise, living alone, self-reported health status, antidepressant use, benzodiazepine use, and prescription sleep medication use.

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Table 3

Variability in Objective Sleep Measures and Odds of MCI or Dementia

	Outcome = MCI or Dementia vs. Normal			
	Minimally Adjusted[a]		Multivariate Adjusted[b]	
Predictor (SD over all nights)	**OR (95% CI)**	**Wald χ^2 [1, N=1242], p-value**	**OR (95% CI)**	**Wald χ^2 [1, N=1220], p-value**
Total Sleep Time, minutes				
Q1 (<28.58)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (28.58 to <42.16)	0.81 (0.58-1.14)	1.49, p = 0.22	0.82 (0.58-1.17)	1.21, p = 0.27
Q3 (42.16 to <61.04)	0.96 (0.68-1.34)	0.07, p = 0.79	0.98 (0.69-1.38)	0.02, p = 0.89
Q4 (≥61.04)	1.36 (0.97-1.91)	3.26, p = 0.07	1.40 (0.98-1.98)	3.47, p = 0.06
p-trend		4.02, p = 0.045		4.05, p = 0.04
Sleep Efficiency, %				
Q1 (<2.99)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (2.99 to <4.93)	1.83 (1.30-2.57)	12.00, p = 0.0005	1.89 (1.33-2.69)	12.50, p = 0.0004
Q3 (4.93 to <7.92)	1.43 (1.01-2.02)	4.11, p = 0.04	1.48 (1.04-2.12)	4.60, p = 0.03
Q4 (≥7.92)	1.87 (1.32-2.64)	12.65, p = 0.0004	1.92 (1.34-2.75)	12.74, p = 0.0004
p-trend		8.40, p = 0.004		8.66, p = 0.003
Wake After Sleep Onset, minutes				
Q1 (<11.64)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (11.64 to <20.33)	1.31 (0.94-1.83)	2.52, p = 0.11	1.29 (0.91-1.82)	2.10, p = 0.15
Q3 (20.33 to <37.44)	1.21 (0.86-1.69)	1.17, p = 0.28	1.22 (0.86-1.73)	1.26, p = 0.26
Q4 (≥37.44)	1.24 (0.88-1.75)	1.54, p = 0.21	1.25 (0.87-1.78)	1.48, p = 0.22
p-trend		1.04, p = 0.31		1.11, p = 0.29
Sleep Latency, minutes				
Q1 (<10.10)	1.00 (reference)	- -	1.00 (reference)	- -
Q2 (10.10 to <18.15)	1.00 (0.71-1.40)	0.00, p = 1.00	0.98 (0.69-1.38)	0.02, p = 0.90
Q3 (18.15 to <33.89)	0.94 (0.67-1.32)	0.11, p = 0.74	0.92 (0.65-1.31)	0.20, p = 0.66
Q4 (≥33.89)	1.36 (0.98-1.91)	3.30, p = 0.07	1.37 (0.97-1.94)	3.20, p = 0.07
p-trend		2.66, p = 0.10		2.60, p = 0.11

A separate model was run for each predictor.

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[a] Adjusted for age, race, clinic and education

[b] Adjusted for age, race, clinic, education, body mass index, number of depressive symptoms, comorbidities, number of IADL impairments, smoking status, alcohol use, exercise, living alone, self-reported health status, antidepressant use, benzodiazepine use, and prescription sleep medication use.